Polymorphism in Pharmaceutical Solids

edited by
Harry G. Brittain
Discovery Laboratories, Inc.
Milford, New Jersey

MARCEL DEKKER, INC. NEW YORK • BASEL

ISBN: 0-8247-0237-9

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 44-61-261-8482; fax: 44-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Pref

Since
molecu
proper
metho
the str
extrem
phenor
other r
vent m
I
pound
state p
conduc
crystal
conduc
heat o
phase
determ

Contents

Cont

Harry (
Jersey

Stephen
cognosy,

Eugene
Central F

David J.
macy, U

J. Keith
Iowa Cit

Kenneth
macy, P

Michael
Storrs, C

5

Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids

J. Keith Guillory

The University of Iowa
Iowa City, Iowa

I. METHODS EMPLOYED TO OBTAIN UNIQUE POLYMORPHIC FORMS

Organic medicinal agents that can exist in two or more solid phases often can provide some distinct advantages in particular applications. The metastable solid may be preferred in those instances where absorption of the drug is dissolution rate dependent. The stable phase may be less susceptible to chemical decomposition and may be the only form that can be used in suspension formulations. Often a metastable polymorph can be used in capsules or for tableting, and the thermodynamically stable form for suspensions. Factors related to processing, such as powder flow characteristics, compressibility, filterability, or hygroscopicity, may dictate the use of one polymorph in preference to another. In other cases, a particular form may be selected because of the high reproducibility associated with its isolation in the synthetic procedure.

It is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future syntheses. Conversion from one polymorph to another can occur during processing or upon storage. An additional incentive for

N UNIQUE

two or more solid phases
in particular applications.
se instances where absorp-
ənt. The stable phase may
tion and may be the only
ations. Often a metastable
bleting, and the thermody-
tors related to processing,
sibility, filterability, or hy-
)lymorph in preference to
ıay be selected because of
isolation in the synthetic

e crystalline material that
)dynamically stable before
)le form may be obtained
oduce the metastable form
)olymorph to another can
ın additional incentive for

isolating and identifying polymorphs that provides certain advantages is the availability of subsidiary patents for desirable polymorphic forms, or for retaining a competitive edge through unpublished knowledge. In 1990 Byrn and Pfeiffer found more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity, recovery, or prevention of precipitation [1].

One question that is likely to arise during the registration process is "What assurance can be provided that no other crystalline forms of this compound exist?" It is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity. This may seem to be a daunting task, particularly in light of the widely quoted statement by Walter C. McCrone [2] that "Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic and inorganic, can crystallize in different crystal forms or polymorphs. In fact, the more diligently any system is studied the larger the number of polymorphs discovered." On the other hand, one can take comfort from the fact that some important pharmaceuticals have been in use for many years and have, at least until now, exhibited only one stable form. Indeed, it seems to this author that there must be particular bonding arrangements of some molecules that are so favorable energetically as to make alternate arrangements unstable or nonisolatable.

In the future, computer programs using force-field optimization should be perfected to the point where it will be possible to predict, with confidence, that a particular crystalline packing arrangement is the most stable that is likely to be found. These programs also may make it possible to predict how many alternate arrangements having somewhat higher energy can potentially be isolated [3,4]. Until that time, the developmental scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found. The situation is further complicated by the phenomenon of "disappearing polymorphs" [5], or metastable crystal forms that seem to disappear in favor of more stable ones.

Some polymorphs can be detected, but not isolated. Hot stage microscopy has been used extensively to study polymorphic transfor-

mations. The microscopist can detect numerous polymorphic transformations, but the individual polymorphs often prove to be so unstable that they cannot be isolated by the usual methods. An excellent example of this is the work of Grießer and Burger on etofylline [6]. These authors identified five polymorphic forms by thermomicroscopy, but only stable Modification I could be obtained by recrystallization, even when seed crystals from the hot stage were used. Similarly, Kuhnert-Brandstätter, Burger, and Völlenklee [7] described six polymorphic forms of piracetam, only three of which could be obtained by solvent crystallization. All the others were found only by crystallization from the melt. What, then, is a careful investigator to do?

In this chapter, the various methods used to isolate polymorphs, hydrates, and solvates will be described. As Bernstein [8] has observed, "The conditions under which different polymorphs are obtained exclusively or together also can provide very useful information about the relative stability of different phases and the methods and techniques that might be necessary to obtain similar structures of different chemical systems." In this context, it is hoped that the following information will prove useful in devising a "screening" protocol for the preparation of the various solid state forms of pharmaceuticals. While one cannot be absolutely certain that no additional forms will be identified in the future, this approach should provide some assurance that "due diligence" has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development and storage.

A. Sublimation

On heating, approximately two-thirds of all organic compounds are converted partially from the solid to the gaseous state and back to solid, i.e., they sublime [9]. While strictly speaking the term sublimation refers only to the phase change from solid to vapor without the intervention of the liquid phase, it is often found that crystals are formed on cooler surfaces in close proximity to the melt of organic compounds when no crystals were formed at temperatures below the melting point. The most comprehensive information concerning sublimation temperatures of compounds of pharmaceutical interest can be found in tables

nerous polymorphic transfor-
often prove to be so unstable
ethods. An excellent example
r on etofylline [6]. These au-
/ thermomicroscopy, but only
/ recrystallization, even when
d. Similarly, Kuhnert-Brand-
ed six polymorphic forms of
tained by solvent crystalliza-
crystallization from the melt.
o?
; used to isolate polymorphs,
s Bernstein [8] has observed,
lymorphs are obtained exclu-
useful information about the
the methods and techniques
structures of different chemi-
hat the following information
" protocol for the preparation
aceuticals. While one cannot
rms will be identified in the
ne assurance that "due dili-
dentify crystalline forms that
se of drug development and

all organic compounds are
seous state and back to solid,
ing the term sublimation re-
vapor without the interven-
that crystals are formed on
melt of organic compounds
ures below the melting point.
erning sublimation tempera-
terest can be found in tables

in the textbook of Kuhnert-Brandstätter [9]. While the information in these tables is designed primarily for the microscopic examination of compounds, it is also possible to utilize it to determine which compounds might be susceptible to the application of techniques (such as vacuum sublimation) that can be carried out on larger scales and at lower temperatures.

The sublimation temperature and the distance of the collecting surface from the material undergoing sublimation have a great influence on the form and size of the crystals produced. The occurrence of polymorphic modifications depends on the temperature of sublimation. In general, it may be assumed that unstable crystals form preferentially at lower temperatures, while at higher temperatures stable forms are to be expected. Nevertheless, mixtures consisting of several modifications are frequently found together. This is the case for barbital and for estradiol benzoate. It should be obvious that the sublimation technique is applicable only to those compounds that are thermally stable.

A simple test can be used to determine if a material sublimes. A small quantity (10–20 mg) of the solid is placed in a petri dish that is covered with an inverted watch glass. The petri dish is heated gently on a hot plate and the watch glass is observed to determine if crystals are growing on it. According to McCrone [2], one of the best methods for obtaining a good sublimate is to spread the material thinly over a portion of a half-slide, cover with a large cover glass, and heat slowly using a Kofler block. When the sublimate is well formed, the cover glass is removed to a clean slide for examination. It is also possible to form good crystals by sublimation from one microscope slide to a second held above it, with the upper slide also being heated so that its temperature is only slightly below that of the lower slide. Cooling of the cover slip by placing drops of various low-boiling solvents on the top surface will cause condensation of the more unstable forms, the lower temperatures leading to the most unstable forms. On a larger scale, a glass cold finger or a commercial sublimator can be employed. Once crystals of various modifications have been obtained, they can be used as seeds for the solution phase crystallization of larger quantities.

Form I of 9,10-anthraquinone-2-carboxylic acid was obtained as needle-like crystals upon sublimation at temperatures exceeding 250°C [10]. Fokkens et al. have used sublimation to purify theophylline for

vapor pressure studies [11]. Sakiyama and Imamura found that stable phases of both 1,3-dimethyluracil and malonamide could be prepared by vacuum sublimation [12].

B. Crystallization from a Single Solvent

Slow solvent evaporation is a valuable method for producing crystals. Solutions of the material being crystallized, preferably saturated or nearly so, are filtered to remove most nuclei and then left undisturbed for a reasonable period of time. The rate of evaporation is adjusted by covering the solution with aluminum foil or Parafilm® containing a few small holes. For a solvent to be useful for recrystallization purposes, the solubility of the solute should be on the order of 5–200 mg/mL at room temperature. If the solubility exceeds 200 mg/mL, the viscosity of the solution will be high, and a glassy product is likely to be obtained. A useful preliminary test can be performed on 25–50 mg of sample, adding a few (5–10) drops of solvent. If all the solid dissolves, the solvent will not be useful for recrystallization purposes. Similarly, highly viscous solvents, and those having low vapor pressures (such as glycerol or dimethylsulfoxide) are not usually conducive to efficient crystallization, filtration, and washing operations. The solvents selected for recrystallization should include any with which the compound will come into contact during synthesis, purification, and processing, as well as solvents having a range of boiling points and polarities. Examples of solvents routinely used for such work are listed in Table 1 together with their boiling points.

The process of solution mediated transformation can be considered the result of two separate events, (a) dissolution of the initial phase, and (b) nucleation/growth of the final, stable phase. If crystals do not grow as expected from a saturated solution, the interior of the vessel can be scratched with a glass rod to induce crystallization by distributing nuclei throughout the solution. Alternatively, crystallization may be promoted by adding nuclei, such as seed crystals of the same material. For example, Suzuki showed that the α-form of inosine could be obtained by crystallization from water, whereas isolation of the β-form required that seeds of the β-form be used [13].

If two polymorphs differ in their melting point by 25–50°C, for

mura found that stable
ıide could be prepared

t

for producing crystals.
referably saturated or
l then left undisturbed
ɔoration is adjusted by
ilm® containing a few
ıllization purposes, the
5–200 mg/mL at room
L, the viscosity of the
cely to be obtained. A
50 mg of sample, add-
dissolves, the solvent
Similarly, highly vis-
ures (such as glycerol
o efficient crystalliza-
vents selected for re-
compound will come
ɔrocessing, as well as
ɔlarities. Examples of
l in Table 1 together

ıation can be consid-
olution of the initial
ıble phase. If crystals
ɔn, the interior of the
ıce crystallization by
rnatively, crystalliza-
s seed crystals of the
the α-form of inosine
whereas isolation of
used [13].
oint by 25–50°C, for

Table 1 Solvents Often Used in the Preparation of Polymorphs

Solvent	Boiling point (°C)
Dimethylformamide	153
Acetic acid	118
Water	100
1-Propanol	97
2-Propanol	83
Acetonitrile	82
2-Butanone	80
Ethyl acetate	77
Ethanol	78
Isopropyl ether	68
Hexane	69
Methanol	65
Acetone	57
Methylene chloride	40
Diethyl ether	35

monotropic polymorphs the lower melting, more soluble, form will be difficult to crystallize. The smaller the difference between the two melting points, the more easily unstable or metastable forms can be obtained.

A commonly used crystallization method involves controlled temperature change. Slow cooling of a hot, saturated solution can be effective in producing crystals if the compound is more soluble at higher temperatures; alternatively, slow warming can be applied if the compound is less soluble at higher temperatures. Sometimes it is preferable to heat the solution to boiling, filter to remove excess solute, then quench cool using an ice bath or even a dry ice–acetone bath. High boiling solvents can be useful to produce metastable polymorphs. McCrone [2] describes the use of high boiling solvents such as benzyl alcohol or nitrobenzene for recrystallization on a hot stage. Behme et al. [14] showed that when buspirone hydrochloride is crystallized above 95°C the higher melting form is obtained; below 95°C the lower

melting form is obtained. Thus the lower melting polymorph could be converted to the higher melting polymorph by recrystallizing from xylene (boiling point 137–140°C).

To understand how temperature influences the composition of crystals that form, it is useful to examine typical solubility–temperature diagrams for substances exhibiting monotropic and enantiotropic behavior [15]. In Fig. 1a, Form II, having the lower solubility, is more stable than Form I. These two noninterchangeable polymorphs are monotropic over the entire temperature range shown. For indomethacin, such a relationship exists between Forms I and II, and between Forms II and III.

In Fig. 1b, Form II is stable at temperatures below the transition temperature T_t, and Form I is stable above T_t. At the transition temperature the two forms have the same solubility, and reversible transformation between enantiotropic Forms I and II can be achieved by temperature manipulation. The relative solubility of two polymorphs is a

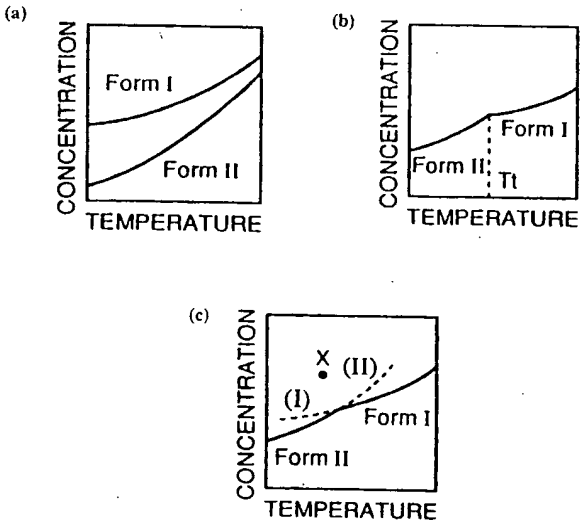
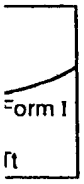


Fig. 1 Solubility curves exhibiting (a) monotropy, (b) enantiotropy, and (c) enantiotropy with metastable phases. (Reprinted with permission of the copyright holder [15].)

nelting polymorph could be
ı by recrystallizing from xy-

luences the composition of
pical solubility–temperature
ropic and enantiotropic be-
ıe lower solubility, is more
ıgeable polymorphs are mo-
: shown. For indomethacin,
and II, and between Forms

:ratures below the transition
T_t. At the transition tempera-
, and reversible transforma-
:an be achieved by tempera-
y of two polymorphs is a



ropy, (b) enantiotropy, and (c)
1 with permission of the copy-

convenient measure of their relative free energies. The polymorph having the lower solubility is the more thermodynamically stable form, i.e., the form with the lower free energy at the temperature of the solubility measurement. At room temperature, carbamazepine Form I (m.p. 189°C) is more soluble than is Form III (m.p. 174°C), so the form with the higher melting point is more soluble. The polymorphs are enantiotropic with respect to each other [16].

There are situations in which kinetic factors can for a time override thermodynamic considerations. Figure 1c depicts the intervention of metastable phases (the broken line extensions to the two solubility curves). If a solution of composition and temperature represented by point X (supersaturated with respect to both I and II) is allowed to crystallize, it would not be unusual if the metastable Form I crystallized out first even though the temperature would suggest that Form II would be the more stable (i.e., less soluble) form. This is an extension of Ostwald's law of stages [17], which states that "when leaving an unstable state, a system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy." This form then transforms to the next most soluble form through a process of dissolution and crystallization. Crystallization of Form I when Form II is more stable would be expected if Form I had the faster nucleation and/or crystal growth rate. However, if the crystals of Form I were kept in contact with the mother liquor, transformation could occur as the more soluble Form I crystals dissolve and the less soluble Form II crystals nucleate and grow. For crystals that exhibit this type of behavior, it is important to isolate the metastable crystals from the solvent by rapid filtration so that phase transformation will not occur.

In the general case, if there are any other polymorphic forms with solubilities below that of Form II, the above-described process will continue between each successive pair of forms until the system finally contains only the most stable (the least soluble) form. The implication of this hypothesis is that, by controlling supersaturation and by harvesting crystals at an appropriate time, it should be possible to isolate the different polymorphic forms. Furthermore, the theory predicts that at equilibrium the product of any crystallization experiment must be the stable form, regardless of the solvent system. It is apparent, however,

from the literature that for some solutes it is the choice of solvent rather than the effects of supersaturation that determines the form that crystallizes [18].

Crystallization of mannitol as a single solute was found to be influenced by both the initial mannitol concentration and by the rate of freezing [19]. In the range of 2.5% to 15%, the δ-polymorph is favored by higher concentrations, whereas the β-polymorph is favored at lower concentrations. At constant mannitol concentration (10%), the α-polymorph is favored by a slow freezing rate, whereas the δ-polymorph is favored by a fast freezing rate.

Kaneko et al. [20] observed that both the cooling rate and the initial concentration of stearic acid in *n*-hexane solutions influenced the proportion of polymorphs A, B, C, and E that could be isolated. Garti et al. [21] reported that for stearic acid polymorphs crystallized from various organic solvents, a correlation was observed between the polymorph isolated and the extent of solvent–solute interaction.

The reason for using crystallization solvents having varying polarities is that molecules in solution often tend to form different types of hydrogen-bonded aggregates, and that these aggregate precursors are related to the crystal structures that develop in the supersaturated solution [22]. Crystal structure analysis of acetanilide shows that a hydrogen-bonded chain of molecules is aligned along the needle axis of the crystals. This pattern is characteristic of secondary amides that crystallize in a trans conformation so that the carbonyl acceptor group and the –NH hydrogen bond donor are anti to one another. The morphology of acetanilide crystals can be controlled by choosing solvents that promote or inhibit the formation of this hydrogen-bond chain. Hydrophobic solvents such as benzene and carbon tetrachloride will not participate in hydrogen-bond formation, so they will induce the formation of rapidly growing chains of hydrogen-bonded amides. Crystals grown by evaporation methods from benzene or carbon tetrachloride are long needles. Solvents that are proton donors or proton acceptors inhibit chain formation by competing with amide molecules for hydrogen-bonding sites. Thus acetone inhibits chain growth at the –NH end, and methanol inhibits chain growth at the carbonyl end of the chain. Both solvents encourage the formation of rod-like acetanilide crystals, while

the choice of solvent rather
mines the form that crystal-

;le solute was found to be
ıcentration and by the rate
5%, the δ-polymorph is fa-
he β-polymorph is favored
ol concentration (10%), the
ş rate, whereas the δ-poly-

h the cooling rate and the
exane solutions influenced
l E that could be isolated.
id polymorphs crystallized
was observed between the
nt–solute interaction.
)lvents having varying po-
:nd to form different types
hese aggregate precursors
elop in the supersaturated
:etanilide shows that a hy-
d along the needle axis of
econdary amides that crys-
rbonyl acceptor group and
: another. The morphology
hoosing solvents that pro-
:n-bond chain. Hydropho-
achloride will not partici-
ll induce the formation of
l amides. Crystals grown
bon tetrachloride are long
proton acceptors inhibit
molecules for hydrogen-
owth at the –NH end, and
ıyl end of the chain. Both
acetanilide crystals, while

mixtures of benzene and acetone give hybrid crystals that are rod-shaped, with fine needles growing on the ends [23].

Some solvents favor the crystallization of a particular form or forms because they selectively adsorb to certain faces of some polymorphs, thereby either inhibiting their nucleation or retarding their growth to the advantage of others. Among the factors affecting the types of crystal formed are (a) the solvent composition or polarity, (b) the concentration or degree of supersaturation, (c) the temperature, including cooling rate and the cooling profile, (d) additives, (e) the presence of seeds, (f) pH, especially for salt crystallization, and (g) agitation [22].

Martínez-Ohárriz et al. [24] found that Form III of diflunisal is obtained from polar solvents, whereas Forms I and IV are obtained from nonpolar solvents. Likewise, Wu et al. [25] observed that when moricizine hydrochloride is recrystallized from relatively polar solvents (ethanol, acetone, and acetonitrile), Form I is obtained, whereas nonpolar solvents (methylene chloride or methylene chloride/ethyl acetate) yield Form II.

In determining what solvents to use for crystallization, one should be careful to select those likely to be encountered during formulation and processing. Typically these are water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, and hexane. Matsuda employed 27 organic solvents to prepare two polymorphs and six solvates of piretanide [26].

According to McCrone [27], in a poor solvent the rate of transformation of a metastable to a more stable polymorph is slower. Hence a metastable form once crystallized can be isolated and dried before it is converted to a more stable phase by solution phase mediated transformation. In some systems the metastable form is extremely unstable and may be prepared only with more extreme supercooling. This is usually performed on a very small scale with high boiling liquids so that a saturated solution at a high temperature that is suddenly cooled to room temperature will achieve a high degree of supersaturation [28].

There are many examples in the literature of the use of single solvents as crystallization screens. Slow crystallization from acetone, acetonitrile, alcohols, or mixtures of solvents yields the Form A of

fosinopril sodium, but rapid drying of a solution of this compound yields Form B, sometimes contaminated with a small amount of Form A [29]. A rotary evaporator can be used to maintain a solution at the appropriate temperature as solvent is being removed.

Form I of dehydroepiandrosterone was obtained by recrystallization from warm ethyl acetate, acetone, acetonitrile, or 2-propanol. Form II was obtained by rapid evaporation, using a vacuum from solutions in dioxane, tetrahydrofuran, or chloroform (which are higher boiling, less polar solvents) [30].

C. Evaporation from a Binary Mixture of Solvents

If single-solvent solutions do not yield the desired phase, mixtures of solvents can be tried. Multicomponent solvent evaporation methods depend on the difference in the solubility of the solute in various solvents. In this approach, a second solvent in which the solute is sparingly soluble is added to a saturated solution of the compound in a good solvent. Often a solvent system is selected in which the solute is more soluble in the component with the higher vapor pressure. As the solution evaporates, the volume of the solution is reduced and, because the solvents evaporate at different rates, the composition of the solvent mixture changes.

Occasionally, crystals are obtained by heating the solid in one solvent and then pouring the solution into another solvent or over cracked ice. Otsuka et al. [31] obtained phenobarbital Form B by adding dropwise a saturated solution of the compound in methanol to water at room temperature. Form E was obtained by the same technique, but by using a saturated solution of phenobarbital in dioxane.

Kitamura et al. have shown that the fraction of Form A of *L*-histidine decreases quickly when the volume fraction of ethanol in an ethanol–water solvent system increases above 0.2, and that pure Form B is obtained at a 0.4 volume fraction of ethanol [32]. The transformation rate for conversion of Form B to Form A decreases with ethanol concentration. The authors postulated that the concentration of the conformer that corresponds to Form A decreases more with ethanol concentration than that of Form B, and so the growth rate of Form A will also decrease.

lution of this compound
a small amount of Form
naintain a solution at the
removed.
obtained by recrystalliza-
itrile, or 2-propanol. Form
a vacuum from solutions
which are higher boiling,

e of Solvents

esired phase, mixtures of
t evaporation methods de-
solute in various solvents.
ıe solute is sparingly solu-
npound in a good solvent.
the solute is more soluble
ıre. As the solution evapo-
and, because the solvents
n of the solvent mixture

heating the solid in one
another solvent or over
obarbital Form B by add-
ound in methanol to water
y the same technique, but
al in dioxane.
raction of Form A of *L*-
fraction of ethanol in an
e 0.2, and that pure Form
ınol [32]. The transforma-
A decreases with ethanol
concentration of the con-
s more with ethanol con-
owth rate of Form A will

An example of precipitation in the presence of a second solvent is seen in the case of indomethacin. The γ-crystal form of indomethacin can be obtained by recrystallization from ethyl ether at room temperature, but the α-form is prepared by dissolution in methanol and precipitation with water at room temperature [33]. Precipitation can also result from the addition of a less polar solvent. Form II of midodrine hydrochloride, metastable with respect to Form I, can be prepared by precipitation from a methanolic solution by means of a less polar solvent such as ethyl acetate or dichloromethane [34].

In Fig. 2, three crystalline modifications of thalidomide are illustrated. These were obtained by solvent recrystallization techniques and differ both in crystal habit and in crystal structure. Two of the forms were obtained from a single solvent, and one from a binary mixture.

D. Vapor Diffusion

In the vapor diffusion method, a solution of the solute in a good solvent is placed in a small, open container that is then stored in a larger vessel containing a small amount of a miscible, volatile nonsolvent. The larger vessel (often a desiccator) is then tightly closed. As solvent equilibrium is approached, the nonsolvent diffuses through the vapor phase into the solution, and saturation or supersaturation is achieved. The solubility of the compound in a precipitant used in a two-solvent crystallization method such as vapor diffusion should be as low as possible (much less than 1 mg/mL), and the precipitant (the solvent in which the compound is poorly soluble) should be miscible with the solvent and the saturated solution. The most frequent application of this technique is in the preparation of single crystals for crystallographic analysis. An illustration of the technique is provided in Fig. 3 [35].

E. Thermal Treatment

Frequently when using differential scanning calorimetry as an analysis technique, one can observe an endothermic peak corresponding to a phase transition, followed by a second endothermic peak corresponding to melting. Sometimes there is an exothermic peak between the two endotherms, representing a crystallization step. In these cases it is often

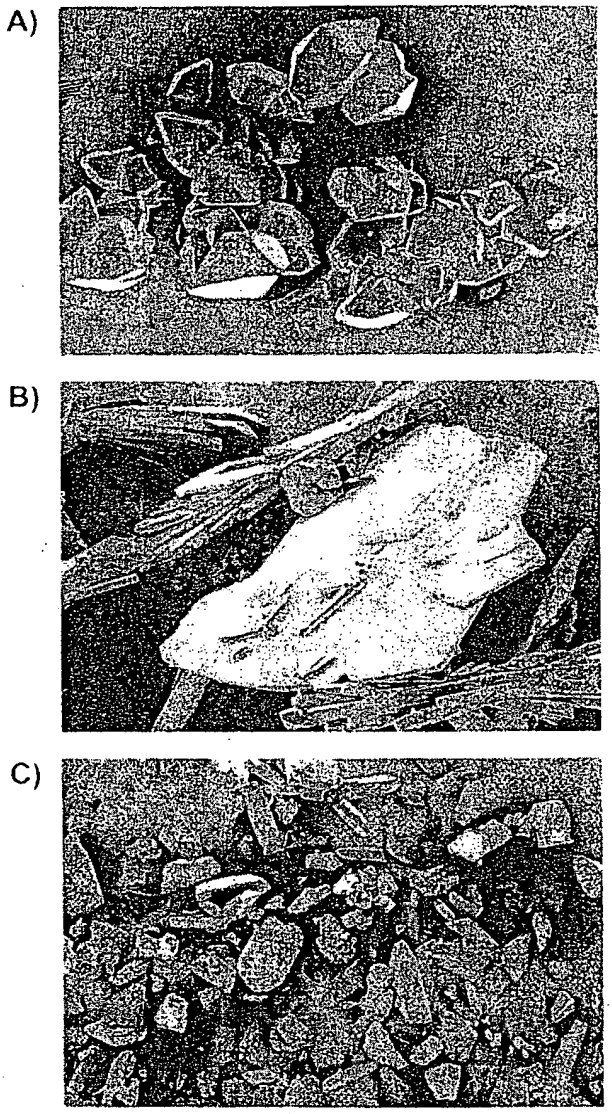


Fig. 2 Three crystalline modifications of thalidomide obtained by solvent recrystallization. (A) Form I obtained as bipyramids by slow crystallization of thalidomide in 1:1 dimethylformamide:ethanol at room temperature. (B) Form II obtained by immersing a saturated solution of thalidomide in acetonitrile in an ice bath. (C) Form III prepared as tabular crystals from a solution in boiling 1,4-dioxane, filtered, then allowed to cool to room temperature. (Photomicrographs courtesy of Dr. S. A. Botha, the University of Iowa.)

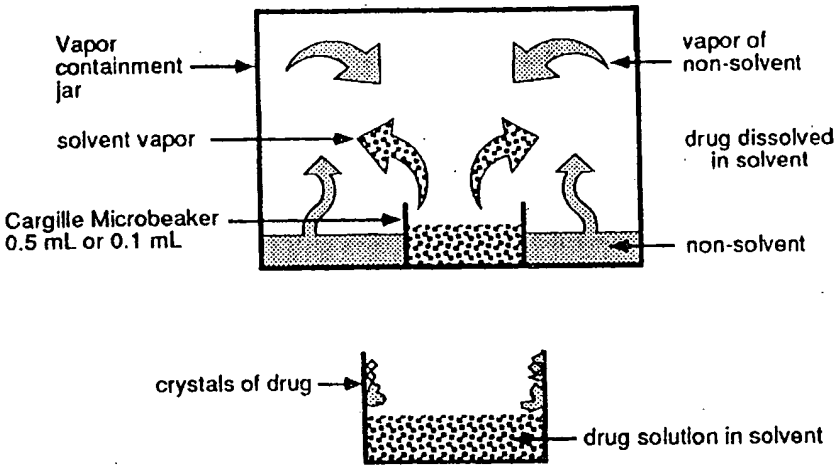


Fig. 3 Crystallization by vapor diffusion. (Reproduced with permission of the author [35] and the copyright holder, Pfizer, Inc.)

possible to prepare the higher melting polymorph by thermal treatment. Thus chlorpropamide Form A is obtained by recrystallization from ethanol solution, but Form C is obtained by heating Form A in an oven maintained at 100°C for 3 hours [36]. While the β-form of tegafur is obtained by the evaporation of a saturated methanol solution, the γ-form is obtained by heating the β-form at 130°C for one hour [37]. Form II of caffeine is prepared by recrystallization from distilled water, but Form I is prepared by heating Form II at 180°C for 10 hours [38].

F. Crystallization from the Melt

In accordance with Ostwald's rule [17], the cooling of melts of polymorphic substances often first yields the least stable modification, which subsequently rearranges into the stable modification in stages. Since the metastable form will have the lower melting point, it follows that supercooling is necessary to crystallize it from the melt. After melting, the system must be supercooled below the melting point of the metastable form, while at the same time the crystallization of the more stable form or forms must be prevented. Quench cooling a melt can

lomide obtained by solvent
nids by slow crystallization
ıl at room temperature. (B)
ın of thalidomide in acetoni-
ılar crystals from a solution
cool to room temperature.
the University of Iowa.)

sometimes result in formation of an amorphous solid that on subsequent heating undergoes a glass transition followed by crystallization [39].

On a somewhat larger scale, one can use a vacuum drying pistol and a high boiling liquid such as chlorobenzene to achieve the desired end. Form II of *p*-(1*R*,3*S*)-3-thioanisoyl-1,2,-2-trimethylcyclopentane carboxylic acid was obtained by recrystallization from a 50:50 v/v benzene:petroleum ether mixture. Form I then was obtained by melting Form II in the vacuum drying pistol [40]. Caffeine Form I is prepared by heating Form II at 180°C for 10 hours [38]. Yoshioka et al. [41] observed that when the amorphous solidified melt of indomethacin was stored at 40°C, it partly crystallized as the thermodynamically stable γ-form. Yet at 50°C, 60°C, and 70°C, mixtures of the α- and the γ-form were obtained. Sulfathiazole Form I is obtained by heating Form III crystals (grown from a dilute ammonium hydroxide solution at room temperature) at 170°C for 30–40 minutes [42].

G. Rapidly Changing Solution pH to Precipitate Acidic or Basic Substances

Many drug substances fall in the category of slightly soluble weak acids, or slightly soluble weak bases, whose salt forms are much more soluble in water. Upon addition of acid to an aqueous solution of a soluble salt of a weak acid, or upon addition of alkali to an aqueous solution of a soluble salt of a weak base, crystals often result. These crystals may be different from those obtained by solvent crystallization of the weak acid or weak base. Nucleation does not necessarily commence as soon as the reactants are mixed, unless the level of supersaturation is high, and the mixing stage may be followed by an appreciable time lag before the first crystals can be detected. Well-formed crystals are more likely to result in these instances than when rapid precipitation occurs.

Form I of the x-ray contrast agent iopanoic acid was prepared [43] by dissolving the acid in 0.1 N NaOH, adjusting the pH to 12.5, bubbling nitrogen into the solution, and adding 0.1 N hydrochloric acid until the pH reached 2.15. The resulting precipitate was vacuum filtered

ıs solid that on subsequent
d by crystallization [39].
se a vacuum drying pistol
ene to achieve the desired
,-2-trimethylcyclopentane
zation from a 50:50 v/v
n was obtained by melting
ıffeine Form I is prepared
38]. Yoshioka et al. [41]
melt of indomethacin was
thermodynamically stable
ures of the α- and the γ-
obtained by heating Form
ıydroxide solution at room
42].

Precipitate

of slightly soluble weak
salt forms are much more
an aqueous solution of a
n of alkali to an aqueous
ystals often result. These
l by solvent crystallization
loes not necessarily com-
less the level of supersatu-
ollowed by an appreciable
ted. Well-formed crystals
n when rapid precipitation

panoic acid was prepared
adjusting the pH to 12.5,
ıg 0.1 N hydrochloric acid
pitate was vacuum filtered

and stored *in vacuo* (380 torr) for 12 hours at 35°C. Similarly, Form III of hydrochlorothiazide was precipitated from sodium hydroxide aqueous solution by the addition of hydrochloric acid [44].

When piretanide was dissolved in 0.1 N NaOH at room temperature and acid was added in a 1:1 ratio (to pH 3.3), piretanide Form C precipitated. However, when the base:acid ratio used was 1:0.95, a mixture of amorphous piretanide and Form C precipitated [45].

H. Thermal Desolvation of Crystalline Solvates

The term "desolvated solvates" has been applied to compounds that were originally crystallized as solvates but from which the solvent has been removed (generally by vaporization induced by heat and vacuum). Frequently, these "desolvated solvates" retain the crystal structure of the original solvate form and exhibit relatively small changes in lattice parameters. For this reason, these types have been referred to as pseudopolymorphic solvates. However, in instances where the solvent serves to stabilize the lattice, the process of desolvation may produce a change in lattice parameters, resulting in the formation of either a new crystal form or an amorphous form. These solvates have been referred to as polymorphic solvates. Byrn [46] has characterized the desolvation of polymorphic solvates as occurring in four steps, (a) molecular loosening, (b) breaking of the host–solvent hydrogen bonds (or other associations), (c) solid solution formation, and (d) separation of the product phase.

The process of desolvating pseudopolymorphic solvates is simpler, involving only the two steps of (a) molecular loosening and (b) breaking of host–solvent hydrogen bonds or associations. Byrn [46] has summarized the desolvation studies performed on caffeine hydrate, theophylline hydrate, thymine hydrate, cytosine hydrate, dihydrophenylalanine hydrate, dialuric acid hydrate, cycloserine hydrate, erythromycin hydrate, fenoprofen hydrate, manganous formate dehydrate, bis(salicylaldehyde) ethylenediamine cobalt (II) chloroformate, cephatoglycine hydrates and solvates, and cephalexin solvates and hydrates. Among factors that influence the desolvation reaction are the appearance of defects, the size of tunnels in the crystal packing arrange-

ment, and the strength of hydrogen bonding between the compound and its solvent of crystallization [46].

Rocco et al. [47] obtained Form II of zanoterone by recrystallization from ethanol and vacuum drying at 45°C. Form III was isolated by desolvating the acetonitrile solvate form at 80°C under vacuum, and this was the form chosen for use in the clinical drug product due to the high reproducibility of its isolation during manufacture. Similarly, Forms I and II of stanozolol were obtained by heating solvates of the compound to 205°C and 130°C, respectively [48].

The benzene solvate of iopanoic acid was prepared by rapidly freezing a warm benzene solution of iopanoic acid in a dry ice–acetone mixture [43]. The solid obtained was permitted to melt at room temperature, yielding crystals of the solvate suspended in benzene. When these were vacuum filtered and stored *in vacuo* (380 torr) for 12 hours at 70°C, Form II was obtained free of benzene.

Dehydration of hydrates can also lead to the formation of unique crystals. Caffeine Form II was prepared by recrystallizing caffeine from water, drying for 8 days at 30°C, and then heating for 4 hours at 80°C [38]. Chloroquine diphosphate 3:1 hydrate was converted to the anhydrous form at temperatures above 188°C [49]. Etoposide Form I (a monohydrate) was found to undergo a dehydration reaction in the temperature range of 85–115°C to yield etoposide Form 1a. This form could be melted at 198°C and transformed to etoposide Form IIa, which itself melted at 198°C and crystallized to still another polymorph, etoposide Form IIa at 206°C. Etoposide Form IIa was found to melt at 269°C and convert to its hydrated form, etoposide Form II, when exposed to the atmosphere at room temperature. This hydrate was also found to undergo a dehydration reaction at 90–120°C to yield etoposide Form IIa [50].

Differential scanning calorimetry (DSC) curves of levofloxacin hemihydrate measured under various conditions showed different thermograms. This behavior was attributed to the dehydration process that resulted in a multiple-phase transition. Dehydration at higher temperatures (above 70°C) gave a sharp endothermic peak in the DSC thermogram due to the melting of the γ-form, and at a lower temperature (50°C) it led to the observation of a sharp endothermic peak due to the

ing between the compound

zanoterone by recrystalliza-
45°C. Form III was isolated
ı at 80°C under vacuum, and
:linical drug product due to
ring manufacture. Similarly,
d by heating solvates of the
ely [48].
id was prepared by rapidly
ɔic acid in a dry ice–acetone
tted to melt at room temper-
ıded in benzene. When these
› (380 torr) for 12 hours at
ne.
ł to the formation of unique
recrystallizing caffeine from
heating for 4 hours at 80°C
: was converted to the anhy-
[49]. Etoposide Form I (a
ydration reaction in the tem-
poside Form 1a. This form
o etoposide Form IIa, which
till another polymorph, eto-
m IIa was found to melt at
toposide Form II, when ex-
ture. This hydrate was also
90–120°C to yield etoposide

SC) curves of levofloxacin
tions showed different ther-
the dehydration process that
ıydration at higher tempera-
ıic peak in the DSC thermo-
ınd at a lower temperature
ndothermic peak due to the

melting of the α-form. In contrast, the thermal behavior of levofloxacin monohydrate was not affected by dehydration [51].

I. Growth in the Presence of Additives

The presence of impurities can have a profound effect on the growth of crystals. Some impurities can inhibit growth completely, and some may enhance growth. Still others may exert a highly selective effect, acting only on certain crystallographic faces and thus modifying the crystal habit. Some impurities can exert an influence at very low concentrations (less than 1 part per million), whereas others need to be present in fairly large amounts to have any effect [15].

Additives can be designed to bind specifically to the surfaces of particular polymorphs and so inhibit their achieving the critical size for nucleation, allowing a desired phase to grow without competition [52]. Lahav and coworkers have shown that additives at levels as low as 0.03% can inhibit nucleation and crystal growth of a stable polymorph, thus favoring the growth of a metastable polymorph [53]. They also showed that it is possible to design crystal nucleation inhibitors to control polymorphism.

Davey et al. found that Form I crystals of terephthalic acid could be obtained by crystallization only in the presence of *p*-toluic acid [54]. Form II, the more stable polymorph at ambient temperatures, was recovered from a hydrothermal recrystallization experiment.

Ikeda et al. [55] determined that indomethacin can exist in three different crystal forms, denoted α-, β-, and γ-, with the α-form possessing a higher solubility than the γ-form. On recrystallization, crystals of the α-form were the first to be deposited, but these converted gradually to the less soluble γ-form. However, in the presence of hydroxypropyl methylcellulose, conversion from the α-form to the γ-form was inhibited, leading to an increase in the solubility of indomethacin.

While the α-form of glycine normally is obtained by recrystallization from water, 3% of racemic hexafluorovaline leads to the precipitation of the γ-polymorph as trigonal pyramids [56]. This additive was designed to be strongly adsorbed at the four {011} crystal faces of the α-form and to bind at only one pole of the polar crystal, thus leaving

the crystal free to grow at the opposite pole. Since it is bound at the slow growing NH_3^+ end of the polar axis, it does not interfere with the fast growing CO_2^- end.

J. Grinding

Polymorphic transformations have been observed to occur on grinding of certain materials, such as sulfathiazole, barbital, phenylbutazone, cephalexin, chloramphenicol palmitate, indomethacin, and chlorpropamide. Byrn [46] has stated that polymorphic transformations in the solid state require the three steps of (a) molecular loosening (nucleation by separation from the lattice), (b) solid solution formation, and (c) separation of the product (crystallization of the new phase). Depending on the material and the conditions employed, grinding can result in conversion to an amorphous substance. With the exercise of care, different polymorphic forms can be obtained. Otsuka et al. [57] showed that metastable Forms B and C of chloramphenicol palmitate were transformed into stable Form A upon grinding at room temperature. Indomethacin was transformed into a noncrystalline solid during grinding at 4°C, and into metastable Form A by grinding at 30°C. Caffeine Form II is converted into Form I with grinding, and a 95% phase conversion was obtained following 60 hours of grinding time [38].

II. METHODS EMPLOYED TO OBTAIN HYDRATE FORMS

Pharmaceutical solids may come into contact with water during processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating, or spray-drying. Moreover, they may be exposed to water during storage in an atmosphere containing water vapor, or in a dosage form consisting of materials that contain water (e.g., excipients) and are capable of transferring it to other ingredients. Water may be adsorbed onto the solid surface and/or may be absorbed in the bulk solid structure. When water is incorporated into the crystal lattice of the compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates [58]. More than 90 hydrates

ıle. Since it is bound at the
t does not interfere with the

ıserved to occur on grinding
:, barbital, phenylbutazone,
domethacin, and chlorprop-
phic transformations in the
ecular loosening (nucleation
solution formation, and (c)
the new phase). Depending
yed, grinding can result in
ith the exercise of care, dif-
. Otsuka et al. [57] showed
amphenicol palmitate were
ıding at room temperature.
ystalline solid during grind-
grinding at 30°C. Caffeine
ding, and a 95% phase con-
of grinding time [38].

AIN HYDRATE

tact with water during pro-
hilization, wet granulation,
eover, they may be exposed
containing water vapor, or
t contain water (e.g., excipi-
ther ingredients. Water may
nay be absorbed in the bulk
d into the crystal lattice of
ıs, the molecular adduct or
58]. More than 90 hydrates

are described in various USP monographs. Hydrates can be prepared by recrystallization from water or from mixed aqueous solvents. They can also result, in some instances, from exposure of crystal solvates (such as methanolates or ethanolates) to an atmosphere containing water vapor.

Crystalline substances often form with water molecules located at specific sites in the crystal lattice, which are held in coordination complexes around lattice cations. This type of water is denoted as water of crystallization and is common for inorganic compounds. For example, nickel sulfate forms a well-defined hexahydrate, where the waters of hydration are bound directly to the Ni(II) ion. Extraneous inclusion of water molecules can occur if a coprecipitated cation carries solvation molecules with it. Water also can be incorporated into random pockets as a result of physical entrapment of the mother liquor. Well-defined multiple hydrate species can also form with organic molecules. For example, raffinose forms a pentahydrate.

Although most hydrates exhibit a whole-number-ratio stoichiometry, an unusual case is the metastable hydrate of caffeine, which contains only 0.8 moles of water per mole of caffeine. Only in a saturated water vapor atmosphere will additional amounts of water be adsorbed at the surface of the 4/5-hydrate to yield a 5/6 hydrate [59].

In some instances, a compound of a given hydration state may crystallize in more than one form, so that the hydrates themselves exhibit polymorphism. One such example is nitrofurantoin, which forms two monohydrates that have distinctly different temperatures and enthalpies of dehydration. The monohydrates have quite different packing arrangements, with Form I possessing a layer structure and Form II exhibiting a herringbone motif. The included water molecules play a major role in stabilizing the crystal structures. Whereas water molecules are contained in isolated cavities in Form II, in Form I they are located in continuous channels, and this apparently facilitates the escape of water when these crystals are heated [60].

Another example of hydrate polymorphism is amiloride hydrochloride [61], which can be obtained in two polymorphic dihydrate forms. These forms are indistinguishable by techniques other than x-ray powder diffraction.

It is interesting that scopolamine hydrobromide has been reported

to exist as the anhydrous form, a ''hemihydrate,'' a sesquihydrate, and a trihydrate [62], while the unit cell parameters and the molecular geometry of these are all the same as those of the hemihydrate. This finding suggests that the ''hemihydrate'' is actually a partially desolvated sesquihydrate.

Ouabaine is another example of a compound that exhibits many different hydration levels, the most hydrated form being stable at the lowest temperature. Thus the nonahydrate phase of ouabaine is obtained from water at 0–15°C, the octahydrate phase at 15–28°C, and the dihydrate phase at 28–90°C. In addition, ouabaine phases corresponding to 4.5 H_2O, 4 H_2O, and 3 H_2O may be obtained from mixtures of water with other solvents. The anhydrous phase of ouabaine anhydrate is crystallized from ethanol at high temperatures [63].

Typically, hydrates are obtained by recrystallization from water. For example, trazodone hydrochloride tetrahydrate was prepared by dissolving the anhydrate in hot distilled water, allowing the solution to remain at room temperature overnight, and storing the collected crystals at 75% relative humidity and 25°C until they reached constant weight [64].

Hydrates can sometimes be obtained by simply suspending the anhydrous material in water, whereupon a form of Ostwald ripening occurs. For instance, aqueous suspensions of anhydrous metronidazole benzoate are metastable, and storage at temperatures lower then 38°C leads to monohydrate formation accompanied by crystal growth [65]. Sorbitol provides another example of this behavior, where slow cooling of a saturated aqueous solution yields long thin needles of sorbitol hydrate [66]. When suspended in water, anhydrous carbamazepine is transformed to carbamazepine dihydrate [67]. In other instances, hydrates can be obtained from mixed solvent systems. Acemetacin monohydrate can be obtained by slow evaporation from a mixture of acetone and water at room temperature [68].

Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate. On exposure to a relative humidity of 100%, dexmedetomidine hydrochloride is converted to a monohydrate [69]. Droloxifene citrate is an example of a compound that is not very hygroscopic and yet forms a hydrate. Only after storage of the anhydrous form at 85% relative humidity does some sorption of

irate," a sesquihydrate, and
ımeters and the molecular
e of the hemihydrate. This
; actually a partially desol-

ınpound that exhibits many
ed form being stable at the
: phase of ouabaine is ob-
ate phase at 15–28°C, and
on, ouabaine phases corre-
y be obtained from mixtures
ıs phase of ouabaine anhy-
emperatures [63].
ecrystallization from water.
rahydrate was prepared by
ater, allowing the solution
d storing the collected crys-
ıntil they reached constant

by simply suspending the
ı form of Ostwald ripening
of anhydrous metronidazole
ınperatures lower then 38°C
ıied by crystal growth [65].
ehavior, where slow cooling
thin needles of sorbitol hy-
ıhydrous carbamazepine is
57]. In other instances, hy-
systems. Acemetacin mono-
n from a mixture of acetone

er to high relative humidity
On exposure to a relative
ochloride is converted to a
ın example of a compound
ı hydrate. Only after storage
ıidity does some sorption of

water occur. The monohydrate phase can be formed by exposing the anhydrous form to 98% relative humidity for ten days at 24°C [70].

III. METHODS EMPLOYED TO OBTAIN SOLVATE FORMS

Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules, either entrapped within empty spaces in the lattice or interacting via hydrogen bonding or van der Waals force with molecules constituting the crystal lattice. Solvent molecules also can be found in close association with metal ions, completing the coordination sphere of the metal atom. Coordinated solvent molecules are considered as part of the crystallized molecule. A crystal with large empty channels or cavities is not stable because of packing demands. The size and chemical environment of the cavity or channel determine what kind of solvent molecule can be included in the structure and what kind of interaction occurs between solvent and structure.

Depending on the nature of molecular packing arrangements, it may happen that the inclusion of solvent is necessary to build a stable crystal structure. van Geerestein et al. [71] found during numerous crystallization attempts of 11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(I-propynyl) estra-4,9-diene-3-one] that crystals were only obtainable in the presence of *n*-butyl acetate or *n*-propyl acetate. The crystal structure of the compound crystallized from *n*-butyl acetate/methylcyclohexane was solved, and one solvent molecule was found in the crystal structure that showed no strong interactions with the rest of the structure. Apparently, this solvent molecule was necessary to fill empty space resulting after the molecular packing. Solvates in which the solvent fills empty space are generally nonstoichiometric, such as the nonstoichiometric solvates formed by droloxifene citrate with acetonitrile, 2-propanol, ethanol, 1-propanol, and 1-butanol. Typically such solvates exhibit the same x-ray diffraction pattern as does the nonsolvated compound.

When solvent molecules increase the strength of the crystal lattice, they can affect the stability of the compound to solid-state decom-

position. It has been observed that the four solvated and one nonsolvated structures of prenisolone *tert*-butyl acetate affect the flexibility of the steroid nucleus and the structure-dependent degradation of the compound when exposed to air and light [72].

van der Sluis and Kroon found 1,247 different compounds with cocrystallized solvents in the Cambridge Crystallographic Database [73]. Out of 46,460 total structures, they found 9,464 solvate structures, and 95% of these contained one of the 15 solvents given in Table 2.

The most commonly encountered solvates among pharmaceuticals are those of 1 : 1 stoichiometry, but occasionally mixed solvate species are encountered. For structures containing more than one solvent type, one generally finds nonpolar solvents crystallizing together on the one hand and polar solvents on the other. For example, the most common solvents found cocrystallizing with water are (in order of im-

Table 2 Distribution of the 15 Most Abundant Solvents in the Cambridge Crystallographic Database, as the Percentage of Solvate Structures

Solvent	Occurrence (%)
Water	61.4
Methylene dichloride	5.9
Benzene	4.7
Methanol	4.1
Acetone	2.8
Chloroform	2.8
Ethanol	2.6
Tetrahydrofuran	2.3
Toluene	2.2
Acetonitrile	1.9
N,N-dimethylformamide	0.9
Diethyl ether	0.9
Pyridine	0.7
Dimethyl sulfoxide	0.5
Dioxane	0.5

Source: From Ref. 73. Reproduced with permission of the copyright owner.

portance) ethanol, methanol, and acetone. An interesting example of a structure containing a polar and a nonpolar solvent is the sodium salt of the antibiotic K-41, *p*-bromobenzoate monohydrate *n*-hexane solvate [74], which is crystallized from *n*-hexane saturated with water. Perhaps the best known mixed solvate is doxycycline hyclate: (doxycycline · $HCl)_2C_2H_6O$ · H_2O. Triamterene also forms a mixed solvate, containing one *N,N*-dimethylformamide molecule and one water molecule within the crystal lattice [75].

The techniques used to obtain solvates are generally similar to the solvent methods used to obtain polymorphs, i.e. crystallization from a single solvent, from mixed solvents, or by vapor diffusion. Sometimes, it is possible to exchange one solvent within the crystal structure for another. When one recrystallizes a hydrate from dry methanol, in most cases one is left with either a methanol solvate or an anhydrous, unsolvated form of the compound.

A large number of solvates have been reported, especially for steroids and antibiotics. It has been observed that cortisone acetate and dexamethasone acetate can be crystallized as 10 different solvates. Dirithromycin, a semisynthetic macrolide antibiotic, crystallizes in two anhydrous polymorphic forms and in at least nine stoichiometric solvate forms. Six of the known solvates are isomorphic, having nearly identical x-ray powder diffraction patterns [76]. In addition to the anhydrate and dihydrate, erythromycin also forms solvates with acetone, chloroform, ethanol, *n*-butanol, and *i*-propanol [77].

It may be instructive to consider some examples of solvate formation. The compound 5-methoxysulphadiazine forms 1:1 host–guest solvates with dioxane, chloroform, and tetrahydrofuran [78]. These were prepared by heating to boiling a solution of the sulfonamide in the appropriate solvent, followed by slow cooling to obtain large crystals. Spironolactone forms 1:1 solvates with methanol, ethanol, ethyl acetate, and benzene. It also forms a 2:1 spironolactone–acetonitrile solvate [79,80]. The spironolactone solvates were prepared by crystallization in a refrigerator from solutions that were nearly saturated at room temperature.

Another steroid that forms solvates is stanozolol [81]. Solvates having 1:1 stoichiometry were prepared by recrystallization from methanol, ethanol, and 2-propanol, by heating the compound in the

appropriate solvent to 60–70°C and then cooling to 0°C in an ice bath to induce crystallization. The compound also forms a monohydrate and two polymorphs. The polymorphs were prepared by heating the solvates to either 130°C (Form II) or 205°C (Form I).

Mefloquine hydrochloride is an interesting case of a compound that forms stoichiometric 1:1 solvates on cooling hot (50°C) saturated acetone solutions (Form B, acetone solvate 1:1), hot (50°C) saturated isopropanol (Form I, isopropanol solvate 1:1), and a nonstoichiometric ethanol solvate (2.12% ethanol) from hot (50°C) saturated ethanol, Form E, whose x-ray powder pattern does not change following heating to 80°C, in spite of a decrease in the ethanol level to 0.12%. Mefloquine hydrochloride can also be obtained in a nonsolvated form from hot (70°C) saturated acetonitrile (Form A) and as two hemihydrates from water (Forms D and C) prepared at room temperature and at 30°C [82].

IV. METHODS EMPLOYED TO OBTAIN AMORPHOUS MATERIALS

Solids can exist in crystalline or amorphous form. Crystalline materials have defined structures, stoichiometric compositions, and melting points and are characterized by their chemical, thermal, electrical, optical, and mechanical properties [83]. By contrast, amorphous materials have no clearly defined molecular structure and no long-range order, so their structure can be viewed as being similar to that of a frozen liquid but without the thermal fluctuations observed in the liquid phase. As a result, amorphous materials exhibit the classical diffuse "halo" x-ray powder diffraction pattern rather than the sharp peaks observed in the pattern of a crystalline substance. When the halo is broad, it is often difficult to distinguish between a material that is truly amorphous (e.g., a true glass) and one that is merely microcrystalline. This situation exists because when microcrystallites have diameters less than about 50 Å in diameter, a similar "halo" effect is observed.

While crystalline solids offer the advantages of chemical and thermodynamic stability, amorphous solids are occasionally preferred because they undergo dissolution at a faster rate. Rapid dissolution is desirable in the case of solids, which must be dissolved prior to paren-

ıling to 0°C in an ice bath
forms a monohydrate and
pared by heating the sol-
orm I).
ting case of a compound
ıling hot (50°C) saturated
1 : 1), hot (50°C) saturated
), and a nonstoichiometric
(50°C) saturated ethanol,
change following heating
evel to 0.12%. Mefloquine
nsolvated form from hot
ıs two hemihydrates from
perature and at 30°C [82].

IN AMORPHOUS

ɔrm. Crystalline materials
mpositions, and melting
l, thermal, electrical, opti-
ast, amorphous materials
and no long-range order,
milar to that of a frozen
served in the liquid phase.
classical diffuse "halo"
the sharp peaks observed
en the halo is broad, it is
al that is truly amorphous
crystalline. This situation
liameters less than about
observed.
ıges of chemical and ther-
ccasionally preferred be-
ate. Rapid dissolution is
dissolved prior to paren-

teral administration. Faster dissolution is also important for poorly soluble compounds administered orally, since there is often a correlation between dissolution rate and bioavailability. In fact, there are instances in which only the amorphous form has adequate bioavailability.

Amorphous solids can be precipitated from solution or obtained from melts of compounds by carrying out the solidification in such a way as to avoid the thermodynamically preferred crystallization process. They also can be prepared by disrupting an existing crystal structure. Excess free energy and entropy are incorporated into solids as they are converted into the amorphous state, since solidification occurs without permitting the molecules to reach their lowest energy states.

A. Solidification of the Melt

Amorphous solids are often created by rapidly cooling a liquid so that crystallization nuclei can neither be created nor grow sufficiently, whereupon the liquid then remains in the fluid state well below the normal freezing point. In principle, a liquid should freeze (crystallize) when cooled to a temperature below its freezing point. However, if the rate of cooling is high relative to the rate of crystallization, then the liquid state can persist well below the normal freezing point. As cooling continues there is a rise in the rate of increase of the viscosity of the supercooled liquid per unit drop in temperature. The initially mobile fluid turns into a syrup, then into a viscoelastic state, and finally into a brittle glass. A glass is, therefore, a supercooled liquid, and is characterized by an extremely high viscosity (typically of the order of 10^{14} Pa · s). Mechanically, if not structurally, glasses can be regarded as solids.

The characteristic temperature below which melted solids must be cooled to form a glass is the glass transition temperature T_g. The glass transition is a dynamic event that occurs at a temperature below which coordinated molecular motion becomes so slow that a liquid can be considered to take on the properties of a solid. While the exact value of this transition temperature depends on the heating rate, the glass transition temperature is generally found to be about two-thirds that of the melting temperature T_m. Glass transition temperatures reported for pharmaceuticals also follow this general rule, as can be seen in the

listing of ten pharmaceuticals that form glasses (Table 3). It is often found that the presence of impurities that facilitate glass formation increases the ratio T_g/T_m either by raising T_g or by lowering T_m. Hence one might wonder if some of the high values in the last column of Table 3 are due to partial decomposition of the drug substance upon melting. Of course, this is an important concern when employing the melt solidification procedure for the preparation of amorphous materials.

There are many examples given in the monograph *Thermomicroscopy in the Analysis of Pharmaceuticals* [9] of other compounds that solidify on the microscope hot stage to form glasses. However, Table 4 contains examples from the literature in which solidification from the melt (either by slow cooling to room temperature or by quench cooling with liquid nitrogen) has been employed as the specific method for obtaining amorphous material.

B. Reduction of Particle Size

Reduction of the particle size of crystalline materials to the microcrystalline level can yield a material incapable of exhibiting an x-ray pow-

Table 3 Pharmaceuticals Forming Glasses above Room Temperature

Compound	T_g(K)	T_m(K)	T_g/T_m
Cholecalciferol	296	352	0.84
Sulfisoxazole	306	460	0.67
Stilbestrol	308	439	0.70
Phenobarbital	321	443	0.72
Quinidine	326	445	0.73
Salicin	333	466	0.71
Sulfathiazole	334	471	0.71
Sulfadimethoxine	339	465	0.73
Dehydrocholic acid	348	502	0.69
17-β-Estradiol	354	445	0.80

Source: Ref. 84.

ɜses (Table 3). It is often
ilitate glass formation in-
ɔr by lowering T_m. Hence
ıes in the last column of
the drug substance upon
ɔern when employing the
.tion of amorphous mate-

ıonograph *Thermomicros-*
of other compounds that
. glasses. However, Table
which solidification from
ɜmperature or by quench
ɣed as the specific method

ıaterials to the microcrys-
: exhibiting an x-ray pow-

ɔve

T_g/T_m
0.84
0.67
0.70
0.72
0.73
0.71
0.71
0.73
0.69
0.80

Table 4 Amorphous Pharmaceuticals Obtained by Solidification from the Melt

Compound	Method used	Reference
Phenylbutazone	Solidification from the melt	[85]
Indomethacin	Quench cooling using liquid nitrogen or slow cooling from the melt over 30 min	[86,87]
Felodipine	Cooling of the melt in liquid nitrogen or at ambient temperature	[88,89]
Nifedipine	Melting at 180°C followed by immersion in liquid nitrogen	[90]
Benperidol	Melt in an oven at 277°C then cool to room temperature	[91]
Acetaminophen	Solidification of the melt at −5°C/min	[92]
Sulfapyridine	Melting any crystalline form and slowly cooling the melt	[93]
Lovostatin	Melting under nitrogen, rapid cooling to 20°C below the glass transition point	[94]

der diffraction pattern. Dialer and Kuessner [95] found that when sucrose was milled in a vibratory ball mill, the ordered crystal was transformed into a glass-like structure. The increase in surface energy of milled sucrose, as measured by heat of solution, could not be accounted for by an increase in surface area alone. Hence milling disrupts the crystal lattice and imparts the excess free energy and entropy associated with amorphous substances.

Particle size reduction can be achieved using a variety of methods. Sometimes it is helpful to carry out the particle size reduction at reduced temperatures, such as at 4°C or at liquid nitrogen temperature, −196°C. In other instances, grinding with an excipient has been employed as a means of obtaining amorphous materials. Cyclodextrins and microcrystalline cellulose have been used for this purpose. It is also possible that the use of polymeric excipients may inhibit crystal growth when the amorphous solid is dissolved in water. Table 5 contains a list of compounds that have been obtained in amorphous, or partly amorphous, form by milling.

Table 5 Amorphous Pharmaceuticals Obtained by Milling

Compound	Method used	Reference
Cimetidine	Milling	[96]
FR76505	Grinding in a ball mill	[97]
Cephalexin	Grinding in an agate centrifugal ball mill for 4 hours	[98]
Indomethacin	Grinding for 4 hours at 4°C in a centrifugal ball mill; grinding the γ-form at 4°C	[57,99]
(*E*)-6-(3,4-Dimethoxyphenyl)-1-ethyl-4-mesitylimino-3-methyl-3,4-dihydro-2(1H)-pyrimidinone	Grinding in a stainless steel shaker ball mill for 60 minutes	[100]
9,3″-Diacetyl-midecamycin	Mixed grinding with polyvinylpyrrolidone or polyvinylpyrrolidone + hydroxypropylmethylcellulose for 9 hours	[101]
Chloramphenicol stearate	Milling in a Pulverisette 5 grinder (Fritsch) (agate mortar and balls) with colloidal silica or microcrystalline cellulose	[102,103]
Calcium gluceptate	Milling in a Pulverisette 2 grinder (Fritsch) (agate mortar and balls) for 4 hours	[104]
Chloramphenicol palmitate	Milling in a Pulverisette 0 grinder (Fritsch) (agate mortar and balls) for 85 hours	[105]
Aspirin	Grinding with adsorbents under reduced pressure	[106]
	Grinding with β-cyclodextrin	[107]
Ibuprofen	Roll mixing with β-cyclodextrin	[108]
Hydrocortisone acetate	Grinding with crystalline cellulose	[109]

by Milling

used	Reference
	[96]
ll mill	[97]
gate centrifu-	[98]
or 4 hours	
ours at 4°C in	[57,99]
all mill; grind-	
at 4°C	
ainless steel	[100]
ill for 60 min-	
with polyvinyl-	[101]
r polyvinylpyr-	
droxypropyl-	
se for 9 hours	
verisette 5	[102,103]
ch) (agate mor-	
with colloidal	
crystalline cel-	
verisette 2	[104]
ch) (agate mor-	
for 4 hours	
verisette 0	[105]
ch) (agate mor-	
for 85 hours	
dsorbents un-	[106]
pressure	
β-cyclodextrin	[107]
th β-cyclodex-	[108]
crystalline cel-	[109]

Table 5 Continued

Compound	Method used	Reference
Digoxin	Milling in a Glen Creston Model M270 ball mill for 8 hours	[110]
	Comminution of 1 g at 196°C for 15 minutes in a freezer mill	[111]
Amobarbital	Ball-milling with methylcellulose, microcrystalline cellulose, or dextran 2000	[112,113]
Acetaminophen	Ball milling for 24 hours with α- and β-cyclodextrin	[114]
6-Methyleneandrosta-1, 4-diene-3,17-dione	Co-grinding with β-cyclodextrin for 2 hours	[115]

C. Spray-Drying

In the pharmaceutical industry, spray-drying is used to dry heat-sensitive pharmaceuticals, to change the physical form of materials for use in tablet and capsule manufacture, and to encapsulate solid and liquid particles. This methodology is also used extensively in the processing of foods [116]. In the spray-drying process, a liquid feed stream is first atomized for maximal air spray contact. The particles are then dried in the airstream in seconds owing to the high surface area in contact with the drying gas. Spray-drying can produce spherical particles that have good flow properties, and the process can be optimized to produce particles of a range of sizes required by the particular application. The process can be run using either aqueous or nonaqueous solutions. Examples of pharmaceuticals obtained in the form of amorphous powders by spray-drying are found in Table 6.

D. Lyophilization

Lyophilization (also known as freeze-drying) is a technique that is widely employed for the preparation of dry powders to be reconstituted at the time of administration. It is a particularly useful technique in the

Table 6 Amorphous Pharmaceuticals Obtained by Spray-Drying

Compound	Method used	Reference
YM022	Spray-drying a methanol solution	[117]
α-Lactose monohydrate	Spray-drying in a Buchi 190	[118]
	Spray-drying a solution or suspension	[119]
4″-O-(4-methoxy-phenyl) acetyltylosin	Spray drying a dichloromethane solution	[120]
Salbutamol sulfate	Spray-drying of an aqueous solution in Buchi 90 spray dryer	[121]
Lactose	Spray-drying an aqueous solution	[118,122]
Furosemide	Spray-drying from a 4:1 chloroform: methanol solution at 50 and 150°C inlet temperature	[123,124]
Digoxin	Spray-drying an aqueous solution containing hydroxypropyl methylcellulose	[125]
Cefazolin sodium	Spray-drying from a 25% aqueous solution with an inlet temperature of 150°C and an outlet temperature of 100°C	[126]
9,3″-Diacetyl-midecamycin	Spray-drying of aqueous solution in the presence and absence of ethylcellulose	[127]

case of compounds that are susceptible to decomposition in the presence of moisture but that are more stable as dry solids. The physical form, chemical stability, and dissolution characteristics of lyophilized products can be influenced by the conditions of the freeze-drying cycle. In most pharmaceutical applications, lyophilization is performed on aqueous solutions containing bulking agents, and these often are chosen so as to form a coherent cake after completion of the freeze-drying process. However, lyophilization also can be employed to convert crystalline materials into their amorphous counterparts. The lyophilization process usually consists of the three stages of freezing, primary drying,

ed by Spray-Drying

l used	Reference
ıethanol solu-	[117]
: Buchi 190	[118]
ılution or sus-	[119]
chloromethane	[120]
n aqueous solu-	[121]
0 spray dryer	
ıqueous solu-	[118,122]
n a 4:1 chloro-	[123,124]
l solution at 50	
t temperature	
ıqueous solu-	[125]
hydroxypropyl	
n a 25% aque-	[126]
th an inlet tem-	
°C and an out-	
of 100°C	
queous solution	[127]
and absence of	

lecomposition in the pres-
s dry solids. The physical
ıracteristics of lyophilized
of the freeze-drying cycle.
ılization is performed on
and these often are chosen
ɛtion of the freeze-drying
employed to convert crys-
ɛrparts. The lyophilization
f freezing, primary drying,

and secondary drying. For the preparation of amorphous materials, rapid freezing is employed so as to avoid the crystallization process. Both aqueous solutions and solutions containing organic solvents have been lyophilized. The primary drying phase involves sublimation of frozen water or vaporization of another solvent. This step is carried out by reducing the pressure in the chamber and supplying heat to the product. The secondary drying phase consists of the desorption of moisture (or residual solvent) from the solid.

Recently, excipients of various types have been employed in frozen solutions so as to inhibit crystallization. Cyclodextrins appear to be particularly useful for this purpose, although it is generally necessary to employ rapid freezing to liquid nitrogen temperatures to ensure that the freeze-dried product is noncrystalline. When α-cyclodextrin, which has a larger cavity than does β-cyclodextrin, is frozen at a relatively slow rate, it will cocrystallize with compounds such as benzoic acid, salicylic acid, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, and methyl *p*-hydroxybenzoate [128]. However, rapid freezing of a methyl *p*-hydroxybenzoate solution containing α-cyclodextrin at a benzoate/cyclodextrin ratio of 0.33 yields an amorphous solid after freeze-drying [29].

β-Cyclodextrin and its derivatives have been shown to form amorphous lyophilized products with a number of compounds, principally nonsteroidal antiinflammatory agents. Examples from the literature of excipients and pharmaceuticals prepared as amorphous materials by lyophilization are given in Table 7.

E. Removal of Solvent from a Solvate or Hydrate

Solids can sometimes be rendered amorphous by the simple expedient of allowing solvent molecules of crystallization to evaporate at modest temperatures. If the solvent merely occupies channels in the crystal structure, the structure often remains intact, but when the solvent is strongly bonded to molecules of the host, the structure frequently will collapse when the solvent is removed and one obtains an amorphous powder. A few examples of amorphous solids obtained in this manner are found in Table 8.

Table 7 Amorphous Pharmaceuticals Obtained by Lyophilization

Compound	Method used	Reference
Lactose	Lyophilization of a 5% Aqueous Solution	[130]
MK-0591	Lyophilization	[131]
Raffinose	Lyophilization of a 10% aqueous solution frozen at −45°C	[132]
Sucrose	Lyophilization of 10% aqueous solutions	[133]
Dirithromycin	Freeze-drying from methylene chloride solution	[134]
Cefalexin	Aqueous solution frozen at −196°C, then freeze-dried	[135]
	Lyophilization of a saturated aqueous solution	[136]
Calcium gluceptate	Freeze-drying from 2% aqueous solution	[137]
Griseofulvin	Freeze-drying of solutions of griseofulvin or of solutions of mixtures of griseofulvin and mannitol in dioxane or 1:1 dioxane-water with fast freezing in liquid nitrogen	[138]
Tolobuterol hydrochloride	Freeze-drying of aqueous solution	[139]
E1040	Freeze-drying of aqueous solution	[140]
Glutathione	Freeze-drying of a 5% aqueous solution	[141]
Aspirin	Freeze drying of an aqueous solution in the presence of 1.0% hydroxypropyl-β-cyclodextrin	[142]
Ketoprofen	Freeze-drying in the presence of heptakis-(2,6-O-dimethyl)-β-cyclodextrin	[143]
	Freeze-drying with β-cyclodextrin (rapid freezing with liquid nitrogen)	[144]
Glibenclamide	Freezing at liquid nitrogen temperature, freeze-drying over 24 hours	[145]

ned by Lyophilization

d used	Reference
f a 5% Aqueous	[130]
	[131]
f a 10% aqueous	[132]
ı at −45°C	
f 10% aqueous	[133]
ɔm methylene	[134]
on	
ı frozen at	[135]
freeze-dried	
f a saturated aque-	[136]
ɔm 2% aqueous	[137]
solutions of	[138]
r of solutions of	
iseofulvin and	
oxane or 1:1 di-	
vith fast freezing	
gen	
aqueous solution	[139]
aqueous solution	[140]
a 5% aqueous	[141]
an aqueous solu-	[142]
sence of 1.0% hy-	
ɔ-cyclodextrin	
the presence of	[143]
O-dimethyl)-β-	
ith β-cyclodextrin	[144]
g with liquid nitro-	
d nitrogen temper-	[145]
drying over 24	

Table 7 Continued

Compound	Method used	Reference
Naproxen	Colyophilization (223K and 0.013 torr) of naproxen and hydroxyethyl-β-cyclodextrin, or hydroxypropyl-β-cyclodextrin	[146]
Sodium ethacrynate	Rapid freezing of an aqueous solution to −50°C, followed by freeze-drying	[147]
p-Aminosalicylic acid	Colyophilization of *p*-aminosalicylic acid in aqueous solution with pullulan	[148]
Ceftazidime	Freeze-drying a nearly saturated aqueous solution of the free acid	[149]
Cefaclor	Freeze-drying from a nearly saturated aqueous solution	[149]
Cephalothin sodium	Freeze-drying from a 25% aqueous solution	[149]
Cefamandol sodium	Freeze-drying from a 25% aqueous solution	[149]
Cefazolin sodium	Freeze-drying an aqueous solution at low temperature	[149]
Nicotinic acid	Freeze-drying in the presence of β-cyclodextrin (fast-freezing); and heptakis (2,6-O-dimethyl)-β-cyclodextrin	[150]

F. Precipitation of Acids or Bases by Change in pH

If the level of supersaturation is carefully controlled, it is often possible to avoid crystallization when a water-soluble salt of a weak acid is precipitated with a base, or when a water-soluble salt of a weak base is precipitated with an acid. When crystalline iopanoic acid is dissolved in 0.1 N NaOH, and 0.1 N HCl is added, an amorphous powder is precipitated [43]. A similar phenomenon is observed in the case of the precipitation of piretanide [155]. Another example in this genre is the

Table 8 Amorphous Pharmaceuticals Obtained by Solvent Removal

Compound	Method used	Reference
Tranilast anhydrate	Dehydration of the monohydrate over P_2O_5	[151]
Raffinose	Lyophilization and heat drying of the pentahydrate	[132]
Erythromycin	Heating the dihydrate for 2 hours at 135°C in an oven, and then cooling to room temperature	[152,153]
Calcium DL-pantothenate	Drying the methanol:water 4:1 solvate *in vacuo* at 50–80°C	[154]

precipitation of amorphous calcium carbonate, which occurs when a calcium chloride solution is combined with a sodium carbonate solution at 283K [156].

G. Miscellaneous Methods

Earlier during the discussion on the preparation of polymorphs, the doping of crystals was mentioned as a technique for encouraging the formation of one type of polymorph over another. Similarly, if a dopant is employed at levels that will disrupt the crystal lattice, the substance can be made to solidify as an amorphous material. Duddu and Grant [157] observed changes in the enthalpy of fusion of (−)-ephedrinium 2-naphthatenesulfonate when the opposite enantiomer, (+)-ephedrinium 2-naphthalenesulfonate, was added as a dopant.

When *m*-cresol was added to a suspension of insulinotropin crystals grown from a normal saline solution, the crystals were immediately rendered amorphous. It was postulated [158] that the *m*-cresol molecules diffused into the crystals through solvent channels and disturbed the lattice interactions that ordinarily maintained the integrity of the crystal. When zinc acetate or zinc chloride was added to the suspension, the zinc ion stabilized the crystal lattice so that the subsequent addition of *m*-cresol did not alter the integrity of the crystals.

Sometimes solvents exert a similar effect. When a small amount of ethyl acetate is added to a calcium chloride solution prior to addition

of sodium fenoprofen, the calcium fenoprofen that precipitates has a low degree of crystallinity [159]. Similarly, when calcium DL-pantothenate is precipitated from methanol or ethanol solution by the addition of acetone, ether, ethyl acetate, or other solvents, the precipitate obtained is found to be amorphous [154].

V. SUMMARY

The pharmaceutical development scientist who is assigned the task of demonstrating that a substance exhibits only one crystalline form, or that of discovering whether additional forms exist, can utilize the techniques outlined in this chapter as a starting point. Upon completion of this program, one can certainly conclude that due diligence has been employed to isolate and characterize the various solid-state forms of any new chemical entity. One should always be aware that nuclei capable of initiating the crystallization of previously undiscovered forms might be lurking around the laboratory, ready to confound the investigator should their effects become known. In addition, the phenomenon of "disappearing polymorphs" can come into play, and techniques that formerly yielded the same crystals every time may subsequently yield crystals of another, more stable form. In the future, the use of computer simulations of alternative crystallographic structures will suggest how much laboratory work might be required to isolate the polymorphs or solvates of a given compound. Until then, the empirical approach remains superior.

REFERENCES

1. S. R. Byrn, personal communication, October 2, 1996.
2. W. C. McCrone, Jr., *Fusion Methods in Chemical Microscopy*, Interscience, New York, 1957.
3. H. R. Karfunkel, F. J. J. Leusen, and R. J. Gdanitz, *J. Comp.-Aided Mater. Des., 1*, 177 (1993).
4. H. R. Karfunkel, Z. J. Wu, A. Burkhard, G. Rihs, D. Sinnreich, H. M. Buerger, and J. Stanek, *Acta Cryst., B52*, 555 (1996).
5. J. D. Dunitz, and J. Bernstein, *Acc. Chem. Res. 28*, 193 (1995).

6. U. J. Grießer, and A. Burger, *Sci. Pharm., 61*, 133 (1993).
7. M. Kuhnert-Brandstätter, A. Burger, and R. Völlenklee, *Sci. Pharm., 62*, 307 (1994).
8. J. Bernstein, *J. Phys. D: Appl. Phys., 26*, B66 (1993).
9. M. Kuhnert-Brandstätter, *Thermomicroscopy in the Analysis of Pharmaceuticals*, Pergamon Press, Oxford, 1971.
10. S.-Y. Tsai, S.-C. Kuo, and S.-Y. Lin, *J. Pharm. Sci., 82*, 1250 (1993).
11. J. G. Fokkens, J. G. M. van Amelsfoort, C. J. de Blaey, C. G. de Kruif, and J. Wilting, *Int. J. Pharm., 14*, 79 (1983).
12. M. Sakiyama, and A. Imamura, *Thermochim. Acta, 142*, 365 (1989).
13. Y. Suzuki, *Bull. Chem. Soc. Japan, 47*, 2551 (1974).
14. R. J. Behme, T. T. Kensler, D. G. Mikolasek, and G. Douglas, U. S. Patent 4,810,789 (to Bristol-Myers Co.), Mar. 7, 1989.
15. J. W. Mullin, *Crystallization*, 3d ed., Butterworth-Heinemann, Oxford, 1993.
16. R. J. Behme, and D. Brooke, *J. Pharm. Sci., 80*, 986 (1991).
17. W. Ostwald, *Z. Phys. Chem., 22*, 289 (1897).
18. K. K. Nass, "Process Implications of Polymorphism in Organic Compounds," in *Particle Design via Crystallization*, R. Ramanarayanan, W. Kem, M. Larson, and S. Sikdar, eds., AIChE Symposium Series, *284*, 72 (1991).
19. A. J. Kim, and S. L. Nail, Abstract PDD7443, AAPS Annual Meeting: Invited and Contributed Paper Abstracts, Seattle, WA, 1996.
20. F. Kaneko, H. Sakashita, M. Kobayashi, and M. Suzuki, *J. Phys. Chem., 98*, 3801 (1994).
21. N. Garti, E. Wellner, and S. Sarig, *Kristall. Tech., 15*, 1303 (1980).
22. S. R. Byrn, R. R. Pfeiffer, G. Stephenson, D. J. W. Grant, and W. B. Gleason, *Chem. Materials, 6*, 1148 (1994).
23. M. C. Etter, D. A. Jahn, B. S. Donahue, R. B. Johnson, and C. Ojala, *J. Cryst. Growth, 76*, 645 (1986).
24. M. C. Martínez-Ohárriz, M. C. Martin, M. M. Goni, C. Rodriguez-Espinosa, M. C. Tros de Ilarduya-Apaolaza, and M. Sanchez, *J. Pharm. Sci., 83*, 174 (1994).
25. L.-S. Wu, G. Torosian, K. Sigvardson, C. Gerard, and M. A. Hussain, *J. Pharm. Sci., 83*, 1404 (1994).
26. Y. Chikaraishi, A. Sano, T. Tsujiyama, M. Otsuka, and Y. Matsuda, *Chem. Pharm. Bull., 42*, 1123 (1994).
27. W. C. McCrone, "Polymorphism," Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Vol. 11 (D. Fox, M. M. Labes, and A. Weissberger, eds.), Interscience, New York, 1965.

l, 133 (1993).
Völlenklee, *Sci. Pharm.*,

6 (1993).
in the Analysis of Phar-

m. Sci., *82*, 1250 (1993).
de Blaey, C. G. de Kruif,

ı. Acta, 142, 365 (1989).
l (1974).
k, and G. Douglas, U. S.
ır. 7, 1989.
orth-Heinemann, Oxford,

, *80*, 986 (1991).
).
orphism in Organic Com-
ıtion, R. Ramanarayanan,
IChE Symposium Series,

3, AAPS Annual Meeting:
attle, WA, 1996.
and M. Suzuki, *J. Phys.*

Tech., 15, 1303 (1980).
). J. W. Grant, and W. B.

B. Johnson, and C. Ojala,

. M. Goni, C. Rodriguez-
and M. Sanchez, *J. Pharm.*

ierard, and M. A. Hussain,

Otsuka, and Y. Matsuda,

: 8 in *Physics and Chemis-*
Fox, M. M. Labes, and A.
:, 1965.

28. S. Khoshkhoo, and J. Anwar, *J. Phys. D: Appl. Phys., 26*, B90 (1993).
29. H. G. Brittain, K. R. Morris, D. E. Bugay, A. B. Thakur, and A. T. M. Serajuddin, *J. Pharm. Biomed. Anal., 11*, 1063 (1993).
30. L.-C. Chang, M. R. Caira, and J. K. Guillory, *J. Pharm. Sci., 84*, 1169 (1995).
31. M. Otsuka, M. Onoe, and Y. Matsuda, *Drug Dev. Ind. Pharm., 20*, 1453 (1994).
32. M. Kitamura, H. Furukawa, and M. Asaeda, *J. Cryst. Growth, 141*, 193 (1994).
33. N. Kaneniwa, M. Otsuka, and T. Hayashi, *Chem. Pharm. Bull., 33*, 3447 (1985).
34. A. Burger, and A. W. Ratz, *Pharm. Ind. 50*, 1186 (1988).
35. R. F. Shanker, "Micro-Techniques for Physicochemical Measurements," presented at the AAPS Symposium on Pharmaceutical Development Contributions During the Drug Discovery Process, Miami Beach, FL, Nov. 9, 1995.
36. M. Otsuka, and Y. Matsuda, *Drug Dev. Ind. Pharm., 19*, 2241 (1993).
37. T. Uchida, E. Yonemochi, T. Oguchi, K. Terada, K. Yamamoto, and Y. Nakai, *Chem. Pharm. Bull., 41*, 1632 (1993).
38. J. Pirttimäki, E. Laine, J. Ketolainen, and P. Paronen, *Int. J. Pharm., 95*, 93 (1993).
39. B. Peffenot, and G. Widmann, *Thermochim. Acta, 234*, 31 (1994).
40. J. Rambaud, A. Bouassab, B. Pauvert, P. Chevallet, J.-P. Declerq, and A. Terol, *J. Pharm. Sci., 82*, 1262 (1993).
41. M. Yoshioka, B. C. Hancock, and G. Zografi, *J. Pharm. Sci., 83*, 1700 (1995).
42. T. P. Shakhtshneider, and V. V. Boldyrev, *Drug Dev. Ind. Pharm., 19*, 2055 (1993).
43. W. C. Stagner, and J. K. Guillory, *J. Pharm. Sci., 68*, 1005 (1979).
44. B. H. Kim, and J. K. Kim, *Arch. Pharm. Res., 7*, 47 (1984).
45. Y. Chikaraishi, M. Otsuka, and Y. Matsuda, *Chem. Pharm. Bull., 44*, 1614 (1996).
46. Stephen R. Byrn, *Solid State Chemistry of Drugs*, Academic Press, New York, 1982.
47. W. L. Rocco, C. Morphet, and S. M. Laughlin, *Int. J. Pharm., 122*, 17 (1995).
48. W. L. Rocco, *Drug Dev. Ind. Pharm., 20*, 1831 (1994).
49. A.-K. Bjerga Bjaen, K. Nord, S. Furuseth, T. Agren, H. Tønnesen, and J. Karlsen, *Int. J. Pharm., 92*, 183 (1993).
50. B. R. Jasti, J. Du, and R. C. Vasavada, *Int. J. Pharm., 118*, 161 (1995).

51. H. Kitaoka, C. Wada, R. Moroi, and H. Hakusui, *Chem. Pharm. Bull., 43*, 649 (1995).
52. L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil, L. J. W. Shimon, M. Lahav, and L. Leiserowitz, *Angew. Chem., Int. Engl. Ed., 24*, 466 (1985).
53. I. Weissbuch, L. Addadi, M. Lahav, and L. Leiserowitz, *Science, 253*, 637 (1991).
54. R. J. Davey, S. J. Maginn, S. J. Andrews, S. N. Black, A. M. Buckley, D. Cottler, P. Dempsey, R. Plowman, J. E. Rout, D. R. Stanley, and A. Taylor, *J. Chem. Soc. Far. Trans. II, 40*, 1003 (1994).
55. K. Ikeda, I. Saitoh, T. Oguma, and Y. Takagishi, *Chem. Pharm. Bull., 42*, 2320 (1994).
56. I. Weissbuch, L. Leisorowitz, and M. Lahav, *Adv. Materials, 6*, 952 (1994).
57. M. Otsuka, K. Otsuka, and N. Kaneniwa, *Drug Dev. Ind. Pharm., 20*, 1649 (1994).
58. R. K. Khankari, and D. J. W. Grant, *Thermochim. Acta, 248*, 61 (1995).
59. J. Pirttimäki, and E. Laine, *Eur. J. Pharm. Sci., 1*, 203 (1994).
60. M. R. Caira, E. W. Pienaar and A. P. Lötter, *Mol. Cryst. Liquid Cryst., 279*, 241 (1996).
61. M. J. Jozwiakowski, S. O. Williams, and R. D. Hathaway, *Int. J. Pharm., 91*, 195 (1993).
62. A. Michel, M. Drouin, and R. Glaser, *J. Pharm. Sci., 83*, 508 (1994).
63. D. Giron, *Thermochim. Acta, 248*, 1 (1995).
64. K. Sasaki, H. Suzuki, and H. Nakagawa, *Chem. Pharm. Bull., 41*, 325 (1993).
65. M. R. Caira, L. R. Nassimbeni, and B. van Oudtshoorn, *J. Pharm. Sci., 82*, 1006 (1993).
66. H. K. Cammenga, and I. D. Steppuhn, *Thermochim. Acta, 229*, 253 (1993).
67. W. W. L. Young, and R. Suryanarayanan, *J. Pharm. Sci., 80*, 496 (1991).
68. A. Burger, and A. Lettenbichler, *Pharmazie, 48*, 262 (1993).
69. R. Rajala, E. Laine, and G. Örn, *Eur. J. Pharm. Sci., 1*, 219 (1994).
70. A. Burger, and A. Lettenbichler, *Eur. J. Pharm. Biopharm., 39*, 64 (1993).
71. V. J. van Geerestein, J. A. Kanters, P. van der Stuis, and J. Kroon, *Acta Cryst., C42*, 1521 (1986).
72. S. R. Byrn, P. A. Sutton, B. Tobias, J. Frye, and P. Main, *J. Am. Chem. Soc., 110*, 1609 (1988).
73. P. van der Sluis, and J. Kroon, *J. Crystal Growth, 97*, 645 (1989).

l H. Hakusui, *Chem. Pharm. Bull.,*

Weissbuch, J. van Mil, L. J. W.
itz, *Angew. Chem., Int. Engl. Ed.,*

and L. Leiserowitz, *Science, 253,*

rews, S. N. Black, A. M. Buckley,
ın, J. E. Rout, D. R. Stanley, and
ş. *II, 40,* 1003 (1994).
(. Takagishi, *Chem. Pharm. Bull.,*

M. Lahav, *Adv. Materials, 6,* 952

ıiwa, *Drug Dev. Ind. Pharm., 20,*

'hermochim. Acta, 248, 61 (1995).
'harm. Sci., 1, 203 (1994).
Lötter, *Mol. Cryst. Liquid Cryst.,*

ıs, and R. D. Hathaway, *Int. J.*

:, *J. Pharm. Sci., 83,* 508 (1994).
(1995).
wa, *Chem. Pharm. Bull., 41,* 325

. van Oudtshoorn, *J. Pharm. Sci.,*

ın, *Thermochim. Acta, 229,* 253

an, *J. Pharm. Sci., 80,* 496 (1991).
rmazie, 48, 262 (1993).
J. Pharm. Sci., 1, 219 (1994).
r. J. Pharm. Biopharm., 39, 64

P. van der Stuis, and J. Kroon,

Frye, and P. Main, *J. Am. Chem.*

stal Growth, 97, 645 (1989).

74. M. Shiro, H. Nakai, K. Nagashima, and N. Tsuiji, *J. Chem. Soc. Chem. Comm.*, 682 (1978).
75. O. Dahl, K. H. Ziedrich, G. J. Marek, and H. H. Paradies, *J. Pharm. Sci., 78,* 598 (1989).
76. G. A. Stephenson, J. G. Stowell, P. H. Toma, D. E. Dorinan, G. R. Green, and S. R. Byrn, *J. Am. Chem. Soc., 116,* 5766 (1994).
77. Y. Fukumori, T. Fukuda, Y. Yamamoto, Y. Shigitani, Y. Hanyu, T. Takeuchi, and N. Sato, *Chem. Pharm. Bull., 31,* 4029 (1983).
78. M. R. Caira, and R. Mohamed, *Supramol. Chem., 2,* 201 (1993).
79. H. D. Beckstead, G. A. Neville, and H. F. Shurvell, *Fresenius J. Anal. Chem., 345,* 727 (1993).
80. G. A. Neville, H. D. Beckstead, and J. D. Cooney, *Fresenius J. Anal. Chem., 349,* 746 (1994).
81. W. L. Rocco, *Drug Dev. Ind. Pharm., 20,* 1831 (1994).
82. S. Kitamura, L.-C. Chang, and J. K. Guillory, *Int. J. Pharm., 101,* 127 (1994).
83. F. Franks, R. H. M. Hatley, and S. F. Mathias, *Biopharm., 4,* 38, 40–42, 55, (1991).
84. E. Fukuoka, M. Makita, and S. Yamamura, *Chem. Pharm. Bull., 37,* 1047 (1989).
85. B. Perrenot, and G. Widmann, *Thermochim. Acta, 243,* 31 (1994).
86. M. Yoshioka, B. C. Hancock, and G. Zografi, *J. Pharm. Sci., 83,* 1700 (1994).
87. E. Fukuoka, M. Makita and S. Yamamura, *Chem. Pharm. Bull., 34,* 4314 (1986).
88. S. Srčič, J. Kerč, U. Urleb, I. Zupančič, G. Lahajnar, B. Kofler, and J. ŠmidKorbar, *Int. J. Pharm., 87,* 1 (1992).
89. J. Kerc, M. Mohar, and J. Smid-Korbar, *Int. J. Pharm., 68,* 25 (1991).
90. Y. Aso, S. Yoshioka, T. Otsuka, and S. Kojima, *Chem. Pharm. Bull., 43,* 300 (1995).
91. A. E. H. Gassim, P. Girgis Takla, and K. C. James, *Int. J. Pharm., 34,* 23 (1986).
92. E. Nümberg, and A. Hopp, *Pharm. Ind., 44,* 1081 (1982); *45,* 85 (1983).
93. M. W. Gouda, A. R. Ebian, M. A. Moustafa, and S. A. Khalil, *Drug Dev. Ind. Pharm., 3,* 273 (1977).
94. J. P. Elder, *Thermochim. Acta, 166,* 199 (1990).
95. K. Dialer, and K. Kuessner, *Kolloid-S. S. Polymer, 251,* 710 (1973).
96. A. Bauer-Brandl, *Int. J. Pharm., 140,* 195 (1996).
97. A. Miyamae, H. Kema, T. Kawabata, T. Yasuda, M. Otsuka, and Y. Matsuda, *Drug Dev. Ind. Pharm., 20,* 2881 (1994).

98. N. Kaneniwa, K. Imagawa, and M. Otsuka, *Chem. Pharm. Bull., 33*, 802 (1985).
99. M. Otsuka, T. Matsumoto, and N. Kaneniwa, *Chem. Pharm. Bull., 34*, 1784 (1986).
100. A. Miyamae, S. Kitamura, T. Tada, S. Koda, and T. Yasuda, *J. Pharm. Sci., 80*, 995 (1991).
101. T. Sato, M. Ishiwata, S. Nemoto, H. Yamaguchi, T. Kobayashi, K. Sekiguchi, and Y. Tsuda, *Yakuzaigaku, 49*, 70 (1989).
102. F. Forni, G. Coppi, V. Iannuccelli, M. A. Vandelli, and R. Cameroni, *Acta Pharm. Suec., 25*, 173 (1988).
103. F. Fomi, G. Coppi, V. Iannucelli, M. A. Vandelli, and M. T. Bemabei, *Drug Dev. Ind. Pharm., 14*, 633 (1988).
104. R. Suryanarayanan, and A. G. Mitchell, *Int. J. Pharm., 24*, 1 (1985).
105. F. Fomi, V. Iannuccelli, and R. Cameroni, *J. Pharm. Pharmacol., 39*, 1041 (1987).
106. T. Konno, K. Kinuno, and K. Kataoka, *Chem. Pharm. Bull., 34*, 301 (1986).
107. Y. Nakai, *Yakugaku Zasshi, 105*, 801 (1985).
108. Y. Nozawa, K. Suzuki, Y. Sadzuka, A. Miyagishima, and S. Hirota, *Pharm. Acta Helv., 69*, 135 (1994).
109. M. Morita, S. Hirota, K. Kinuno, and K. Kataoka, *Chem. Pharm. Bull., 33*, 795 (1985).
110. A. T. Florence, and E. G. Salole, *J. Pharm. Pharmacol., 28*, 637 (1976).
111. D. B. Black, and E. G. Lovering, *J. Pharm. Pharmacol., 29*, 684 (1977).
112. A. Ikekawa, and S. Hayakawa, *Bull. Chem. Soc. Japan, 55*, 1261 (1982).
113. A. Ikekawa, and S. Hayakawa, *Bull. Chem. Soc. Japan, 55*, 3123 (1982).
114. S.-Y. Lin, and C.-S. Lee, *J. Incl. Phen. Mol. Recogn. Chem., 7*, 477 (1989).
115. C. Torricelli, A. Martini, L. Muggetti, and R. De Ponti, *Int. J. Pharm., 71*, 19 (1991).
116. A. S. Rankell, H. A. Liebermann, and R. F. Schiffman, "Drying," in *The Theory and Practice of Industrial Pharmacy*, 3d ed. (L. Lachman, A. A. Lieberman, and J. L. Kanig, eds.), Lea and Febiger, Philadelphia, 1986, p. 47.
117. K. Yano, N. Takamatsu, S. Yamazaki, K. Sako, S. Nagura, S. Tomizawa, J. Shimaya, and K. Yamamoto, *Yakugaku Zasshi, 116*, 639 (1996).
118. L.-E. Briggner, G. Buckton, K. Bystrom, and P. Darcy, *Int. J. Pharm., 105*, 125 (1994).

M. Otsuka, *Chem. Pharm. Bull., 33*,
. Kaneniwa, *Chem. Pharm. Bull., 34*,
a, S. Koda, and T. Yasuda, *J. Pharm.*
), H. Yamaguchi, T. Kobayashi, K.
igaku, 49, 70 (1989).
i, M. A. Vandelli, and R. Cameroni,
8).
M. A. Vandelli, and M. T. Bemabei,
(1988).
itchell, *Int. J. Pharm., 24*, 1 (1985).
Cameroni, *J. Pharm. Pharmacol., 39*,
ıtaoka, *Chem. Pharm. Bull., 34*, 301
801 (1985).
ıka, A. Miyagishima, and S. Hirota,
4).
and K. Kataoka, *Chem. Pharm. Bull.,*
. *Pharm. Pharmacol., 28*, 637 (1976).
. *Pharm. Pharmacol., 29*, 684 (1977).
Bull. Chem. Soc. Japan, 55, 1261
Bull. Chem. Soc. Japan, 55, 3123
. *Phen. Mol. Recogn. Chem., 7*, 477
getti, and R. De Ponti, *Int. J. Pharm.,*
, and R. F. Schiffman, "Drying," in
trial Pharmacy, 3d ed. (L. Lachman,
, eds.), Lea and Febiger, Philadelphia,
aki, K. Sako, S. Nagura, S. Tomizawa,
ıkugaku Zasshi, 116, 639 (1996).
ystrom, and P. Darcy, *Int. J. Pharm.,*

119. T. Sebhatu, M. Angberg, and C. Ahlneck, *Int. J. Pharm., 104*, 135 (1994).
120. T. Yamaguchi, M. Nishimura, R. Okamoto, T. Takeuchi, and K. Yamamoto, *Int. J. Pharm., 85*, 87 (1992).
121. G. Buckton, P. Darcy, D. Greenleaf, and P. Holbrook, *Int. J. Pharm., 116*, 113 (1995).
122. H. Vromans, G. K. Bolhuis, C. F. Lerk, and K. D. Kussendrager, *Int. J. Pharm., 39*, 201 (1987).
123. Y. Matsuda, M. Otsuka, M. Onoe, and E. Tatsumi, *J. Pharm. Pharmacol., 44*, 627 (1992).
124. Y. Matsuda, M. Otsuka, M. Onoe, and E. Tatsumi, *J. Pharm. Pharmacol., 44*, 627 (1992).
125. E. Nürnberg, B. Dölle, and J. M. Bafort, *Pharm. Ind., 44*, 630 (1982).
126. M. J. Pikal, A. L. Lukes, J. E. Lang, and K. Gaines, *J. Pharm. Sci., 67*, 767 (1978).
127. T. Saito, M. Ishiwata, A. Okada, T. Kobayashi, K. Sekiguchi, and Y. Tsuda, *Yakuzaigaku, 49*, 93 (1989).
128. T. Oguchi, M. Okada, E. Yonemochi, K. Yamamoto, and Y. Nakai, *Int. J. Pharm., 61*, 27 (1990).
129. T. Oguchi, K. Terada, K. Yamamoto, and Y. Nakai, *Chem. Pharm. Bull., 37*, 1881 (1989).
130. L. Figura, *Thermochim. Acta, 222*, 187 (1993).
131. S.-D. Clas, R. Faizer, R. E. O'Connor, and E. B. Vadas, *Int. J. Pharm., 121*, 73 (1995).
132. A. Saleki-Gerhardt, J. G. Stowell, and G. Zografi, *J. Pharm. Sci., 84*, 318 (1995).
133. A. Saleki-Gerhardt, and G. Zografi, *Pharm. Res., 11*, 1166 (1994).
134. G. A. Stephenson, J. G. Stowell, P. H. Toma, D. E. Dorman, J. R. Greene, and S. R. Byrn, *J. Am. Chem. Soc., 116*, 5766 (1994).
135. H. Egawa, S. Maeda, E. Yonemochi, T. Oguchi, K. Yamamoto, and Y. Nakai, *Chem. Pharm. Bull., 40*, 819 (1992).
136. M. Otsuka, and N. Kaneniwa, *Chem. Pharm. Bull., 31*, 4489 (1983).
137. R. Suryanarayanan, and A. G. Mitchell, *Int. J. Pharm., 32*, 213 (1986).
138. K.-H. Frömming, U. Grote, A. Lange, and R. Hosemann, *Pharm. Ind., 48*, 283 (1986).
139. M. Saito, H. Yabu, M. Yamazaki, K. Matsumura, and H. Kato, *Chem. Pharm. Bull., 30*, 652 (1982).
140. K. Ashizawa, K. Uchikawa, T. Hattori, Y. Ishibashi, T. Sato, and Y. Miyake, *J. Pharm. Sci., 78*, 893 (1989).
141. M. Morita, and S. Hirota, *Chem. Pharm. Bull., 30*, 3288 (1982).

142. S. Duddu, and K. Weller, *J. Pharm. Sci., 85*, 345 (1996).
143. O. Funk, L. Schwabe, and K.-H. Frömming, *Drug Dev. Ind. Pharm., 20*, 1957 (1994).
144. O. Funk, L. Schwabe, and K.-H. Frömming, *Pharmazie, 48*, 745 (1993).
145. M. T. Esclusa-Diaz, J. J. Torres-Labandeira, M. Kata, and J. L. Vila-Jato, *Eur. J. Pharm. Sci., 1*, 291 (1994).
146. G. Bettinetti, A. Gazzaniga, P. Mura, F. Giordano, and M. Setti, *Drug Dev. Ind. Pharm., 18*, 39 (1992).
147. R. J. Yarwood, A. J. Phillips, and J. H. Collett, *Drug Dev. Ind. Pharm., 12*, 2157 (1986).
148. T. Oguchi, E. Yonemochi, K. Yamamoto, and Y. Nakai, *Chem. Pharm. Bull., 37*, 3088 (1989).
149. M. J. Pikal, and K. M. Dellerman, *Int. J. Pharm., 50*, 233 (1989).
150. O. Funk, L. Schwabe, and K.-H. Frömming, *J. Incl. Phen. Mol. Recogn. Chem., 16*, 299 (1993).
151. Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Itoh, and Y. Furuyama, *J. Pharm. Sci., 80*, 472 (1991).
152. Y. Fukumori, T. Fukuda, Y. Yamamoto, Y. Shigitani, Y. Hanyu, Y. Takeuchi, and N. Sato, *Chem. Pharm. Bull., 31*, 4029 (1983).
153. E. Laine, P. Kahela, R. Rajala, T. Heiklilä, K. Saamivaara, and I. Piippo, *Int. J. Pharm., 38*, 33 (1987).
154. M. Inagaki, *Chem. Pharm. Bull., 25*, 1001 (1977).
155. Y. Chikaraishi, M. Otsuka, and Y. Matsuda, *Chem. Pharm. Bull., 44*, 1614 (1996).
156. F. A. Andersen, and L. Brecevic, *Acta Chem. Scand., 45*, 1018 (1991).
157. S. P. Duddu, and D. J. W. Grant, *Thermochim. Acta, 248*, 131 (1995).
158. Y. Kim, and A. M. Haren, *Pharm. Res., 12*, 1664 (1995).
159. B. A. Hendriksen, *Int. J. Pharm., 60*, 243 (1990).